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Rapid progression to diabetes in a four-year-old girl with cystic fibrosis

O. PİRGON*, F. CEKMEZ† and E. EREN*

**Department of Pediatric Endocrinology, Konya Education and Research Hospital, Konya; and †Department of Neonatalogy, GATA Medical Faculty, Ankara, Turkey*

Cystic fibrosis (CF) results from mutations in the gene that encodes the CF transmembrane conductance regulator protein located on chromosome 7. This gene encodes a protein that functions as a cyclic adenosine monophosphate-regulated chloride channel. Abnormal function of the channel results in aberrant conductance across the apical membrane of epithelial ductal cells in various organs (e.g., lung, pancreas, sweat gland, liver, nasal mucosa, salivary gland and colon).[1] The usual clinical presentation of CF includes persistent and recurrent pulmonary infection as well as symptoms of pancreatic insufficiency. Cystic fibrosis-induced diabetes can occur at any age, with mean onset reported to be 18–21 year.[2]

Although CF–related diabetes (CFRD) usually presents in the second decade of life, it has been reported in children as young as 10 years.[3] This study describes early-onset diabetes in a four-year-old child with CF complicated with recurrent lung infections that resolved after insulin therapy.

The patient was diagnosed with CF at the age of two after presenting with failure to thrive and respiratory infection. The sweat test revealed sweat chloride concentrations of 85 mmol/L and 72 mmol/L (0–40 mmol/L) in consecutive samples. As genotyping was not available, diagnosis of CF was based on clinical and laboratory values. After implementing substitutional pharmacotherapy in the form of pancreatic enzyme supplementation and inhaled corticosteroid therapy, the patient was in good health. She had a neonatal history of pulmonary artery stenosis and balloon pulmonary angioplasty, and subsequent endovascular stent implantation.

After two uneventfully years, she was hospitalised for recurrent lung infections resistant to antibiotics (teicoplanin and meropenem). Despite high calorific nasogastric and oral feeds, she failed to meet her goal weight. The patient weighted 13 kg (<3rd percentile) and measured 96 centimeters in height (<3rd percentile). On physical examination, she showed respiratory distress in the form of tachypnoea and retractions of the intercostal muscles. Breathing was deep and rapid, while chest auscultation revealed symmetric moderate aeration with crackles, rhonchi and wheezes. Her transcutaneous oxygen saturation was 94% while receiving 6 L/min nasal oxygen. Other systemic examinations were normal. Chest radiograph revealed parenchymal nodular opacities with prominent upper lobe bronchiectasis, consistent with CF (Fig 1a). A computed tomography (CT) scan of the thorax revealed bilateral perihilar consolidation.

Laboratory studies revealed high blood glucose level (412 mg/dL), low serum insulin level (1.64 µiu/mL) with low C-peptide (0.54 ng/mL [0.9–4.2]) level. Her HbAlc was 10.1%. Sedimentation rate was 35 mm/h and C-reactive protein level was 77 mg/dL. Arterial blood gas values showed pH 7.35 and a bicarbonate of 15 mmol/L. Urine and serum ketones were negative. Islet cell antibodies, glutamic acid decarboxylase antibodies and urinary ketones were negative. Subcutaneous insulin was initiated and treatment with benzylpenicillin for 14 days. Her laboratory data and radiological abnormalities markedly improved (Fig 1b). The remainder of the hospital course focused on insulin adjustment and diabetes education for the patient and family. The patient was discharged on multiple daily injections of insulin (0.4 units/kg/day) and pancreatic enzyme supplementations, and her subsequent growth rate improved. At follow-up visits, the patient demonstrated consistent and improved weight gain. At six years of age, she required 0.6 units/kg/day of insulin and had an HbA1c of 7.2%.

As patients with CF are now living longer because of improved medical care, CFRD has become the leading co-

Correspondence to: Dr. Ferhat Cekmez
GATA Medical Faculty, Department of Pediatrics, 34090 Istanbul, Turkey
Email: ferhat_cocuk@hotmail.com

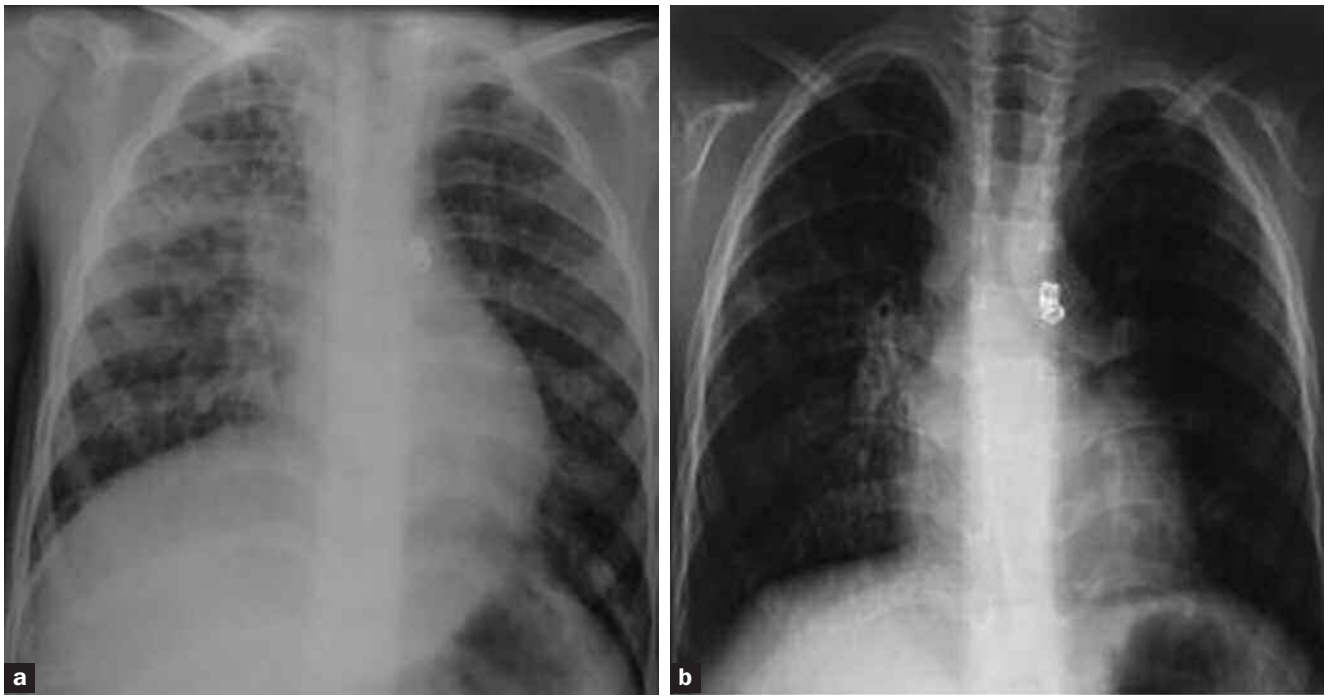

Fig. 1. X-ray images showing **a)** bilateral perihilar consolidation of the thorax, with partial conservation of the apex and basal areas; and **b)** partial resolution two weeks later.

morbidity in patients with CF. Diabetes mellitus occurs in approximately 10% of CF cases, with onset generally after the age of 15 years. Thus, it is seen in 9% of CF children, 26% of adolescents, 35% of adults in the 20–29 age group and 43% of adults aged ≥30.2

There are a few reported cases of CFRD in very young children with CF, with the youngest reported case occurring at 6 months,[4] and another report of a newborn with transient diabetes who later developed impaired glucose tolerance.[5]

The aetiology of CFRD is complex and the mechanisms leading to its development are not fully understood. Although the majority of people with CF develop exocrine pancreatic damage, not all develop glucose intolerance; a second aetiological factor (e.g., genetic susceptibility, autoimmune processes) may determine individual risk of developing CFRD.[6] Although CFRD is a distinct entity, it shares features of type 1 and type 2 diabetes mellitus. Diabetes-associated antibodies are not present.[7–9] All antibodies related to diabetes were negative in the patient reported here; however; C-peptide and insulin levels were low. Microvascular complications (e.g., diabetic retinopathy, neuropathy, nephropathy) have been reported in CFRD. Unlike the situation in type 1 and type 2 diabetes, macrovascular complications such as ischaemic heart disease and stroke are not widely seen in CFRD.

Use of HbA1c screening is not appropriate to test for CFRD, as it is normal in the majority of cases.[10] The patient presented here had severe pneumonia and did not respond to antibiotics and inhaled steroids, but did respond promptly to insulin treatment, achieving very good glycaemic control within days.

Hyperglycaemia may have local and systemic effects, which reduce pulmonary defence against infection. Systemic neutrophil phagocytic activity and chemokinesis are impaired by hyperglycaemia, but function can be restored by rigorous control of blood glucose.[11] Insulin is the only pharmacological treatment recommended, as, in addition to controlling glycaemia, it has positive effects on pulmonary function and nutritional state, and has anti-inflammatory potential. Lanng *et al*.[9] found that insulin therapy reversed negative changes in weight and lung function that began several years before diabetes was diagnosed, suggesting a cause-and-effect relationship between insulin deficiency and CF clinical status.

The Cystic Fibrosis Foundation, following 1998 consensus guidelines,[10] recommends that fasting glucose levels be measured annually, and that fasting and post-prandial levels be measured during hospitalisation for acute illness. However, diabetes may occur earlier and appear soon after the diagnosis of CF. The severity of the insulin secretory defect may also be associated with a poor outcome in CF, including loss of pulmonary function and also higher mortality.

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Talking glucose meter for the visually impaired diabetic patient: the effect of haematocrit on glucose measurement

R. W. A. PEAKE*, M. S. DEVGUN* and I. A. D. O'BRIEN†
*Departments of *Biochemistry and †Medicine, Wishaw General Hospital, Lanarkshire ML2 ODP, UK*

Diabetic retinal disease is a major complication of diabetes and has an incidence of 50–65 per 100,000 in the diabetic population per year in Europe.[1] Anaemia is also a common complication of diabetes mellitus (DM), associated with diabetic nephropathy and chronic kidney disease, resulting in the failure of erythropoietin production.

Among the 29 glucose systems considered in a recent review,[2] only one is listed to have an acoustic mode facility. In recent years, however, attempts have been made to address this problem with the introduction of 'talking' blood glucose monitors, particularly in the USA. In contrast, the UK market contains few options for meters featuring speech output. In the UK, the SCP Talking Meter (BBI Healthcare)[3] became available in April 2006 for use by the visually impaired diabetic patient.

This study describes a 30-year-old male with type 1 DM diagnosed at the age of six. Owing to the occurrence of repeated hypoglycaemic episodes and poor compliance with insulin therapy and diet (body mass index [BMI]: 18) he was issued with an SCP meter. His average glycated haemoglobin (HbA1c) level was approximately 15% (4.8–6.7%), equivalent to 140 mmol/mol (20–42 mmol/mol) on the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) standardised method. He had peripheral neuropathy, significant diabetic nephropathy and developed retinopathy, which progressively limited his vision. On the Snellen scale, his initial visual acuity was 6/60 but seven months later this had deteriorated such that he was only able to count the number of fingers held up in front of him. He was anaemic (Hb: 8–9 g/dL, haematocrit [Hct] 26–28%) and his medication included 200 mg ferrous sulphate (three times a day).

Correspondence to: Dr. M. S. Devgun
Clinical Laboratories, Department of Biochemistry, Wishaw General Hospital, 50 Netherton Street, Wishaw, Lanarkshire ML2 ODP, UK
Email: manjit.devgun@lanarkshire.scot.nhs.uk

Table 1. SensoCard Plus (SCP) and Accu-Check Advantage (ACA) meter: glucose measurements at haematocrit 46% Hb.

Expected (mmol/L)	SCP (mmol/L)	ACA (mmol/L)	SCP minus expected (%)	ACA minus expected (%)
2.5	5.1	5.7	104.0	128.0
5.0	7.0	8.5	40.0	70.0
7.5	8.2	9.5	9.3	26.7
10.0	10.5	11.5	5.0	15.0
12.5	12.0	13.2	–4.0	5.6
15.0	15.0	16.5	0.0	10.0
17.5	17.3	19.2	–1.1	9.7
20.0	20.4	22.1	2.0	10.5

The patient provided Informed consent for this study, which is written following the guidelines issued by the area ethical committee.

In the diabetic clinic the patient's whole-blood glucose was measured by a trained laboratory scientist using the issued SCP meter, and a glucose of 25.8 mmol/L was obtained with acceptable internal quality control performance using the laboratory's standard operating procedure. The same specimen was checked using a ward-based glucose meter (Accu-Check Advantage [ACA], Roche) using a glucose dehydrogenase and coenzyme paraquinone quinoline assay (coefficient of variation [CV] <3.5%), and a glucose of 13.0 mmol/L was observed. This discrepancy was confirmed on a venous sample using the laboratory's routine method (13.2 mmol/L, glucose oxidase assay, CV <2%).

The performance of the patient's SCP meter was assessed by investigating its linearity over a range of glucose and Hct concentrations. First, serial dilutions (n=8, in duplicate) of a patient's whole blood specimen at constant Hct (46%) were spiked with a 0.5 mol/L glucose solution to generate a range of approximately 2.5–20 mmol/L (well within the recommended concentration range for both meters).

The means of the duplicate glucose readings obtained from the SCP and ACA meters were compared using a paired t-test (t=9.22, P<0.0001). Data points from the SCP meter were similar to the expected glucose values; all observations from the ACA meter were positively biased (Table 1). In addition, the ACA results were higher than those obtained with the SCP meter (mean difference: 10.2 %) within the glucose range 10–20 mmol/L.

Overall, acceptable and comparable linearity over the specified range was observed on both machines. Results became increasingly inaccurate when plasma glucose was ≤5.0 mmol/L, with both meters giving higher figures than the values obtained using the laboratory method. This study confirmed the correct functioning of the patient's SCP meter.

The SCP and ACA meters were also tested over a range of Hct values (Table 2). A whole-blood sample was diluted (n=9, in duplicate) in a plasma-based matrix to achieve Hct in the range 19–47% (laboratory reference ranges: males 40–54%, females 37–47%). The observations demonstrated a